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Case Report

White matter abnormality in Jacobsen syndrome assessed by serial MRI

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Abstract

Introduction: Jacobsen syndrome (JS) is caused by a deletion at the terminus of the long arm of chromosome 11. There are few reports of JS associated with cerebral white matter abnormalities (WMA), and the etiology, pathophysiology, and time-dependent changes in WMA with JS still remain unclear.

Case report: The patient was a 2-month-old female with several morphological anomalies, including trigonocephaly, ectropion, flat nasal bridge, low-set ears, and sparse eyebrows. Chromosome analysis (G-banding karyotyping) of 46,XX,del(11)(q23.3) led to the diagnosis of JS. Head MRI performed at age 9 months indicated diffuse WMA with hyperintense signals on T2-weighted imaging. MRI at age 2.5 years demonstrated a decrease in the WMA and progressive myelination.

Discussion: These findings suggested that the WMA in the present patient were due to chronic white matter edema associated with a deletion in the 11q terminal region of *HEPACAM/GlialCAM*, a causative gene for megalencephalic leukoencephalopathy with subcortical cysts type 2B (MLC2B). As with some of MLC2B patients, the WMA in the present patient improved over time. The present report is the first to document dramatic changes in WMA in JS visualized by serial MRI examinations from the neonatal period through early childhood.

Conclusion: The findings of the present study suggested that WMA in JS are due to chronic white matter edema associated with *HEPACAM/GlialCAM* deletion and show gradual improvement over time, as seen in some MLC2B patients.

Keywords: Cerebral white matter abnormality; Jacobsen syndrome; Hepatic and glial cell adhesion molecules (HEPACAM/GlialCAM); Megalencephalic leukoencephalopathy with subcortical cysts type 2B (MLC2B)

1. Introduction

Jacobsen syndrome (JS; #MIM 147791) is caused by a partial deletion at the terminus of the long arm of chromosome 11 and results in morphological anomalies of the skull, face, and limbs, congenital heart disease, and delayed psychomotor development [1,2]. The deletion size is 7–20 Mb, and the proximal break point is located within or towards the telomeric end of subband 11q23.3, with the deletion usually extending to the telomere [1,2]. To date, hundreds of patients with JS have been reported, and its prevalence is estimated

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at 1/100,000 livebirths, with a male/female ratio of 2:1 [2].

There are few reports of cases of JS complicated by cerebral white matter abnormalities (WMA), and the etiology, pathophysiology, and time-dependent changes in the WMA in JS remain unclear. Yamamoto et al. [3] reported that WMA in JS are associated with deletions of *HEPACAM* (#MIM 611642), also called *GlialCAM*, located on 11q24.2. The mutation in *HEPACAM*/*GlialCAM* is responsible for megalencephalic leukoencephalopathy with subcortical cysts type 2A (MLC2A; #MIM 613925) and 2B (MLC2B; #MIM 613926) [4–6]. Moreover, some patients with MLC2B show gradual improvement of the WMA over time [4,6].

The present report is the first to document dramatic changes in WMA in JS visualized by serial MRI examinations from the neonatal period through young childhood.

2. Patient report

The patient, a 2-month-old female with no history of fetal abnormalities, was born at 34 weeks and 3 days of gestation without asphyxia. Her birth weight was 1668 g, her height was 38.5 cm, and her head circumference was 31.0 cm. She was referred to Tokyo Metropolitan Children's Medical Center due to the chief complaint of morphological abnormalities of the skull.

A physical examination showed craniofacial abnormalities, such as trigonocephaly, mild macrocephaly, ectropion, flat nasal bridge, low-set auricles, sparse eyebrows, small ears, and down-slanting palpebral fissures. Widened thumbs and slight hypotonia were also observed. There were no other suspected findings of congenital cytomegalovirus infection, such as auditory abnormalities, chorioretinitis, lung hypoplasia, or hepatosplenomegaly. The blood cell count and results of routine laboratory tests were normal. No abnormality was detected in the neonatal screening for metabolic disease. Chromosome analysis (G-banding karyotyping) detected 46,XX,del(11)(q23.3-qter) (Fig. 1). Based on the latter findings, JS was diagnosed.

At age 9 months, the patient underwent cranioplasty for the trigonocephaly.

A head MRI at age 1 month (1 m) (when the corrected gestational age was 38 weeks), showed diffuse areas of high signal intensity on T2-weighed imaging throughout the cerebral white matter (Fig. 2-A). At age 9 months (9 m), a head MRI indicated extensive WMA in subcortical sites (Fig. 2-B). At age 2-and-a-half years (2y6m), the WMA showed improvement, and myelination had progressed in the subcortical and deep white matter (Fig. 2-C). No cerebral calcification or cortical dysplasia suggestive of congenital infection was found.

The patient's development was delayed; she achieved neck stabilization at age 8 months, was able to speak meaningful words at age 17 months, and was able to stand with support at age 22 months. Currently, at age 3 years, she can walk with support and utter several meaningful words. Her head circumference was about average whereas her body weight and height remained somewhat low (from −1 to −2 SD) during the period. Neither abnormalities on electroencephalogram nor epilepsy onset were observed.

Chromosomal microarray analysis (CMA; CytoScan HD array, Affymetrix®) was performed to analyze for other pathogenic copy number variation (CNV) potentially responsible for the WMA. No pathogenic CNVs were noted except the deletion at the terminal of the 11q region (arr[hg19]11q23.3q25(119,923,669-134,938,470)x1) in line with the results of G-banding. Genetic analyses in this study were approved by the ethics committee of Tokyo Metropolitan Childrens' Medical Center (approval number 2019b-169), and written informed consent was obtained from the patient's parents.

3. Discussion

The present case of JS presenting with WMA was followed up from the neonatal period to young childhood using serial head MRI. The MRI studies demonstrated improvement in the extent of WMA observed at ages 1 and 9 months by age 2 years 6 months. In addition, the patient's development as well as the imaging findings were tracked in detail through the study period. Her psychomotor development showed retardation but continuously improved, as reflected in improvement of the imaging findings. WMA in JS have been reported in only a few cases, and to date, there are no reported instances in early infancy that were assessed by MRI, as shown in Table 1 [3,7–9]. A review of these previous case reports reveals that MRI taken by the age of around 2 shows more extended or diffuse WMA (Table 1). In contrast, after age 2 years, the WMA were mostly mild or partial, and myelination showed progression (Table 1, Fig. 2), suggesting that WMA in JS improve during infancy, as in our patient. The hyperintensity seen on MRI T2 imaging is apparently due to water retention and the immaturity of myelination; however, it should be noted that it was difficult to determine whether the diffuse hyperintensity in the white matter seen in the present patient at age 1 month (when the corrected gestational age was 38 weeks) was due to the genetic abnormality described later or to a physiological change. Nonetheless, the WMA showed clear signs of improvement over time as water retention in the white matter decreased and myelination progressed. The clinical course in the present case differed from that of most

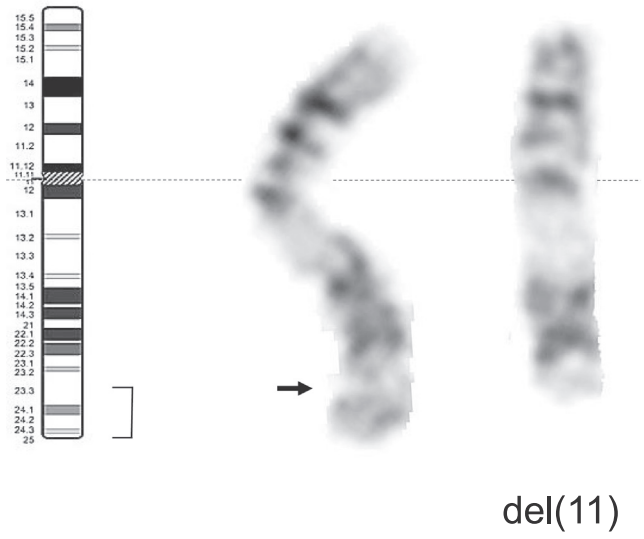

Fig. 1. G-banded partial karyotype in a pair of chromosomes 11. Cytogenetic analysis was performed using a peripheral blood sample from the patient. The terminal deletion of 11q was detected, and the karyotype was 46,XX,del(11)(q23.3). The arrow indicates the break point of the long arm of chromosome 11.

neurodegenerative diseases, leukodystrophies and other irreversible leukoencephalopathies, which cause progressive neurological symptoms, developmental arrest or regression, and exacerbation of cerebral lesions. The importance of the present study lies in its demonstration of dramatic changes in the WMA associated with JS in the same patient from the neonatal period through childhood using MRI.

Yamamoto et al. [3] suggested that the *HEPACAM/GlialCAM* located on 11q24.2 gives rise to white matter lesions. The *HEPACAM/GlialCAM* encodes the hepatic and glial cell adhesion molecule (HEPACAM/GlialCAM) and is the causative gene in MLC2A and MLC2B [4–6]. MLC is characterized by chronic white matter edema, macrocephaly, and frontotemporal and/or frontoparietal subcortical cysts [4–6]. MLC2A is classified as an autosomal recessive disorder and presents a severer phenotype with no improvement in either psychomotor development or WMA while MLC2B is autosomal dominant and presents a milder phenotype with gradual improvement [4–6]. Various types of *HEPACAM/GlialCAM* mutations, such as nonsense, missense, single-base deletion, and frame-shift mutations, have been reported [6]. Although multiple genes encompassed in the deleted region have possibilities to be involved in WMA development, *HEPACAM/GlialCAM* haploinsufficiency in the present patient might have played a potential role in WMA pathogenesis.

WMA associated with JS are thought to be due to white matter water retention and intra-myelinic edema associated with *HEPACAM/GlialCAM* deletion as seen in MLC patients. HEPACAM/GlialCAM molecules are expressed on the cell surface and are involved in the adhesion of glial cells, maintenance of the cytoskeleton, and ion homeostasis [4–6,10]. Previous research has shown that WMA in MLC were attributable to water retention in the white matter, intra-myelinic edema, and myelin vacuolation [4–6]. These findings are consistent with the presumptive cause of white matter T2-hyperintensity in JS. In some MLC2B patients, the WMA, as well as psychomotor deficits, improve over time [4,6]. In such cases, MRI shows diffuse white matter edema in early infancy, the water retention decreases with time, and the white matter lesions also show gradual improvement [4,6]. The improvement seen in many patients with MLC2B occurs between ages 1 year and 4 years [4]. The age-related time course of WMA in MLC2B is similar to that seen in our patient, suggesting that improvements in WMA in JS may reflect an amelioration of white matter water retention and intra-myelinic edema, and may be associated with improvement in psychomotor development.

The reasons why WMA and the subcortical cysts are rare in most patients with JS remain unclear. However, the fact that MLC2B due to a *HEPACAM/GlialCAM* mutation exhibits an autosomal dominant inheritance pattern [4–6] may provide a basis for understanding WMA is rarely associated with JS. The penetrance of a *HEPACAM/GlialCAM* mutation is reportedly variable or low [3,6,9]. In addition, MLC2B phenotypes caused by a *HEPACAM/GlialCAM* mutation might show the variable expressivity generally

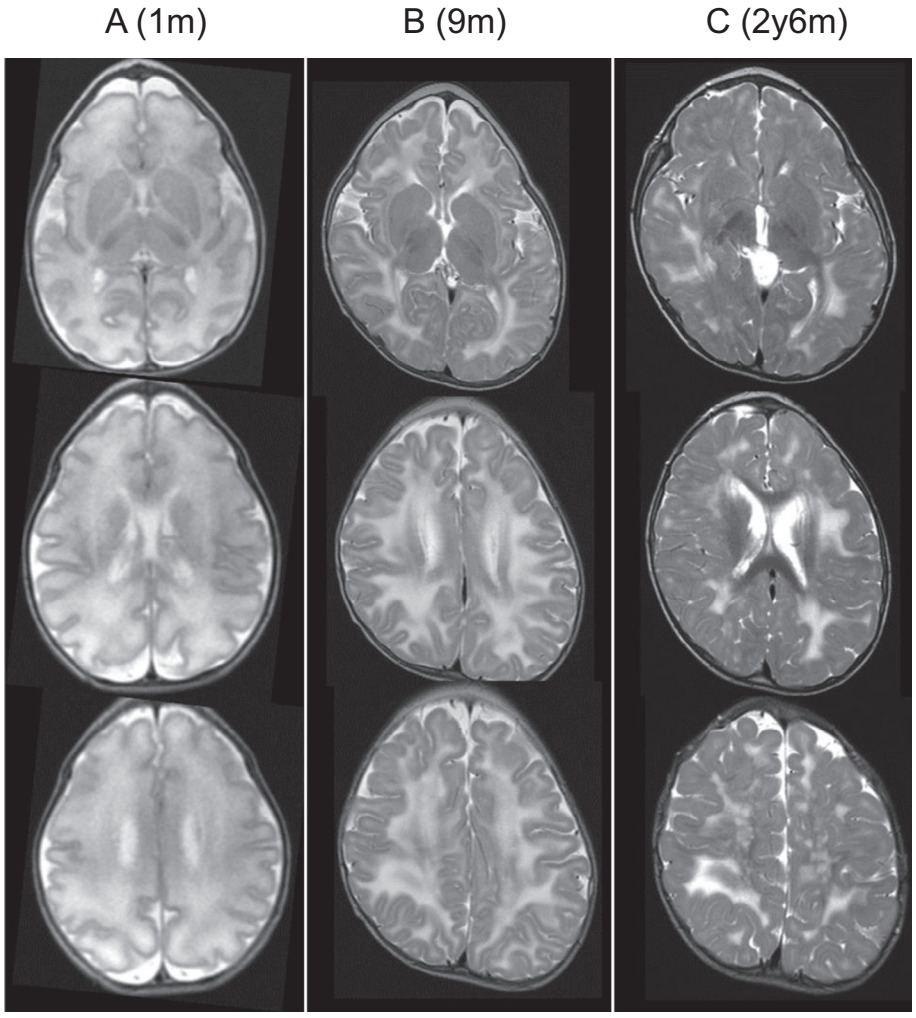

Fig. 2. Serial MRI examinations from the neonatal period through young childhood (T2 weighted image). A, age 1 month (1 m); B, age 9 months (9 m); and C, age 2 years and 6 months (2y6m). At age 1 m (when the corrected age was 38 weeks of gestation), areas of diffuse, high signal intensity were observed throughout the cerebral white matter (A). At 9 m, T2 weighed imaging revealed extensive WMA with high signal intensity in subcortical and deep white matter (B). At age 2y6m, distribution of the WMA decreased and myelination showed progression (C).

Table 1
Changes in the distribution and severity of white matter lesions by age.

No.	MRI timing	WMA distribution	Abnormal karyotype	References
1	1 m*	Diffuse	del(11)(q23.3-qter)	Present case
	9 m*	Extended		
	2y6m*	Partial		
2	1y5m	Diffuse	del(11)(q23.3-qter)	Wardinsky et al. [8]
3	1y8m	Partial	del(11)(q23.3-q24.2)	Yamamoto et al. [3]
4	2y1m	Diffuse	del(11)(q23.3-qter)	Ono et al. [7]
5	2y5m	Partial	del(11)(q23.3-qter)	Ono et al. [7]
	3y6m	Partial		
6	3y8m	Partial	del(11)(q23.3-q25)	Yamamoto et al. [3]
7	30y	Partial	del(11)(q23.3-qter)	Yu et al. [9]

* Time course in the present case. Abbreviation: (age) m, months; y, year; MRI, magnetic resonance imaging; WMA, white matter abnormalities.

common in autosomal dominant diseases. Therefore, it is possible that WMA in patients with JS due to *HEPACAM*/*GlialCAM* deletions may present a wide phenotypic spectrum. Further research is needed to clarify why the WMA phenotype in patients with JS is rare.

4. Conclusion

The findings of the present study suggested that WMA in JS are due to chronic white matter edema associated with *HEPACAM/GlialCAM* deletion and shows gradual improvement over time, as seen in some patients with MLC2B.

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Conflict of interest

The authors declare no competing interests.

Author contributions

Shuhei Fujino, M.D.: Design and conceptualized study; analyzed the data; drafted the manuscript for intellectual content.

Hiroshi Yoshihashi, M.D., Ph.D.: Interpreted the data; revised the manuscript for intellectual content.

Ryojun Takeda, M.D.: Major role in the acquisition of data.

Satoshi Ihara, M.D.: Major role in the acquisition of data.

Sahoko Miyama, M.D., Ph.D.: Interpreted the data; revised the manuscript for intellectual content.

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